REMARKS

Reconsideration of this application is requested. Claims 1-14 and 20-27 are in the case.

I. THE 35 U.S.C. 112, SECOND PARAGRAPH, REJECTION

Claims 1-26 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for the reasons stated on pages 2-4 of the Action. In response, the claims have been amended. The following comments are offered.

In paragraphs 1 and 2, the Examiner has objected to the expressions "as appropriate" and "terminated". In response, Claim 1 has been amended to replace "optionally substituted and/or terminated (as appropriate)" with "optionally substituted". In addition, the expression "substituted and/or terminated" has been replaced by "substituted' in Claims 1 and 23.

With respect to the other claims containing the phrase "as appropriate" (Claim 26 and parts (f) and (q) of Claim 21), it is the Applicants' position that, in those claims, the phrase is intended to acknowledge that, in certain processes, different starting materials may be required to provide different end products. This is clear from the wording of those claims, and no indefiniteness arises with respect to those claims. Reconsideration and withdrawal of this aspect of the formal rejection are accordingly respectfully requested.

In paragraph 3, the term "derivative" has been objected to as allegedly indefinite. In response, without conceding to the merit of this rejection, the term "pharmaceutically acceptable derivative" has been replaced by "salt, solvate or protected derivative". Basis for that amendment may be found, for example, at page 8, line 1 and page 35, lines 18-28.

In paragraph 4, the Examiner alleges that Claim 2 is improperly dependent on Claim 1 as cycloalkyl and oxygen-interrupted alkyl are not amongst the definitions provided in claim 1. This is not correct. The Examiner's attention is directed to the definition of "alkyl" provided at page 8, line 25 to page 9, line 7, which explicitly covers the groups mentioned in Claim 2. Withdrawal of this aspect of the formal rejection is accordingly respectfully requested.

In paragraphs 5-7, the Examiner has objected to the "use" claims. In response, and without conceding to the merit of this rejection, those claims have been canceled without prejudice. New Claim 27 is based on the subject matter of claim 19 and depends on present claim 20. No new matter is entered.

In paragraph 8, the Examiner has objected to the expression "or susceptible to" as allegedly rendering claim 20 indefinite. This rejection is respectfully traversed.

The language objected to by the Examiner would be readily understood by one of ordinary skill in this art. Thus, antiarrhythmic drugs have often been administered on a prophylactic basis (as was done in the Cardiac Arrhythmia Suppression Trial – see page 1, lines 20-26 of the application as filed) to patients who, in the clinical judgment of a physician, are likely to develop an arrhythmia. Thus, one of ordinary skill would fully understand and would be well used to determining which patients are "susceptible to" an arrhythmia.

In paragraph 9, Claims 22-25 have been rejected as allegedly improperly dependent on Claim 21 as there is no provision for protected versions in Claim 21. In response, the rejection with respect to Claim 25 is not understood since that claim does not refer to Claim 21 at all. With regard to Claims 22-24, those claims are, in fact, completely independent of Claim 21. This will be evident from the fact that Claims 22-24 are claims to compounds whereas Claim 21 is a process claim. Claims 22-24 simply refer to claim 21 for definitional purposes. There is no prohibition under U.S. patent law against an independent claim referring to part of the subject matter defined in another independent claim for definitional purposes. In Claims 22-24, the references to Claim 21 merely serve as method of avoiding unnecessary repetition of definitions of basic structural formulae that have already been provided in that claim. Reconsideration and withdrawal of this aspect of the formal rejection are accordingly respectfully requested.

In paragraph 10, Claim 26 has been objected to in view of the words "as defined herein". In response, Claim 26 has been amended to properly define the compounds referred to in the preamble of that claim. Basis for those amendments are to be found, for example, at page 31, line 16 through page 32, line 10 of the application has filed. In order to avoid possible overlap with copending application Serial No. 09/623,707, references to the compounds of formula XVIII and XXVIII have been deleted without prejudice.

In paragraph 11, the Examiner has asserted that it is impossible to tell what is going on in Claim 26 because the reagents to not seem to be related to the final product. In response, the following is drawn to the Examiner's attention:

(a) Compounds of formula VIII may be formed by reaction of a compound of formula XXIX (in which R^Z represents -C(O)XR^1) with a compound of formula XXX in the presence of a formaldehyde; and

(b) Compounds of formula XVII may be formed by reaction of a compound of formula XXIX (in which R^Z represents H) with a compound of formula XXX in the presence of a formaldehyde.

Each of the preparations (a) and (b) above proceeds *via* a "double Mannich" reaction, where each final product is formed by cyclization in the presence of formaldehyde of the intermediate product formed by reaction of the amine with the ketone and one equivalent of formaldehyde. Preparations (a) and (b) are both quite clearly described in Claim 26. Moreover, the skilled person (such as a synthetic organic chemist) would have no difficulty in discerning which of the

alternatives was suitable for the preparation of each final compound mentioned in the preamble to Claim 26. In light of the above, it is clear from Claim 26 how each of the final compounds of that claim are prepared.

Withdrawal of the outstanding 35 U.S.C. § 112, second paragraph, rejection is now believed to be in order. Such action is respectfully requested.

II. THE 35 U.S.C. § 112, FIRST PARAGRAPH, REJECTIONS

Claim 21 stands rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification, while enabling for most aspects, allegedly does not reasonably provide enablement for step (d) for D=H or step (e). That rejection is respectfully traversed.

This allegation appears to be based on the Examiner's belief that it is not possible to reduce a keto group to a methylene group in the presence of a carbamate group. In this respect, it is pointed out that the relevant reductions may, for example, be achieved by using tosylhydrazine and a reducing agent (see page 15, lines 5 to 9 and 16 to 20 of the application as filed) or hydrazine in the presence of a base (i.e. under Wolff-Kischner conditions - see page 15, lines 20 to 21 of the application as filed). It is not true that the (thio)carbamate functionality will necessarily be cleaved under such conditions. This is because of a number of factors, including the fact that the C-atom of the carbonyl group in a

(thio)carbamate is considerably less electropositive (and so less electrophilic) than the C-atom of the carbonyl group in a ketone or ester. As a result, it is perfectly possible to ensure that hydrazine or tosylhydrazine only reacts with (and hence, ultimately, reduces) the ketone or ester group in compounds of formula VII, and not with the carbamate group of such compounds.

Claim 21 is also rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for most aspects, allegedly does not reasonably provide enablement for step (d) for A=fourth choices. This position is respectfully traversed

The Examiner's allegation appears to be based on his belief that it is not possible to reduce an ester to an acyclic ether. In this respect, attention is directed to the attached copy of page 1100, as well as copies of the cover pages, from *Advanced Organic Chemistry* 3rd Ed., J. March, John Wiley and Sons, New York (1985). From the contents of the section entitled *"Reduction of Carboxylic Esters to Ethers"*, it is clear that there are a plethora of agents that are suitable for achieving the supposedly impossible reduction. Moreover, given that *Advanced Organic Chemistry* is very much a "standard" textbook in the field of synthetic organic chemistry, one of ordinary skill would have been well aware of the contents of the enclosed page at the time that the current application was filed. As a result, the specification of this case is clearly enabling in respect of the process objected to by the Examiner.

Claim 21 further stands rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for most aspects, allegedly does not reasonably provide enablement for the scope of (r). In response, in order for step (r) of Claim 21 to be reasonably enabled, it is not necessary for the specification to teach the skilled person how to convert *any* given substituent into any other given substituent. Claim 21(r) merely covers all conversions of R^6 substituents that are known to be possible. The number of known conversions is so large that it would be unfair to expect the applicant to be limited to a list which could only possibly comprise a small selection of these.

Moreover, as the word "conversion" in step (r) may be interpreted to cover multi-step reactions, it is believed that, in fact, there is no case to answer. This is because the skilled person, at the time that this application was filed, would have been aware of a multitude of methods which can be combined to convert any given substituent on a phenyl group to any other given substituent (proceeding, for example, *via* an unsubstituted phenyl group).

Claim 26 stands rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was allegedly not described in the specification in such a way as to enable one skilled in the art to make and use the invention. It appears that this rejection was made based on a misunderstanding of claim 26, as discussed earlier in this response. Reconsideration and withdrawal of the

outstanding rejection of claim 26 are accordingly respectfully requested.

Withdrawal of the 35 U.S.C. § 112, first paragraph, is now believed to be in order. Such action is respectfully requested.

III. THE OBVIOUSNESS REJECTION

Claims 1-10 and 14-26 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Alstermark (U.S. Patent 6,291,475). That rejection is respectfully traversed.

It is not conceded that the invention as claimed in this application is rendered obvious by Alstermark. However, in order to reduce the issues and advance prosecution, Claim 1 has been amended to delete without prejudice C_{1-4} alkyl from the definition of D. The claimed compounds now differ from the compounds disclosed by Alstermark in that, when the group *"D"* represents either H or OH, then at least one of R^{5a} and R^{5b} represents C_{1-3} alkyl or at least one of R^2 and R^3 is other than H or C_{1-4} alkyl. Alstermark neither discloses nor suggests such compounds.

In light of the above, it is clear that one of ordinary skill would not have been motivated to resort to the disclosure of Alstermark. Even if one of ordinary skill had consulted Alstermark, it is clear that presently claimed invention would

not have resulted or have been rendered obvious thereby. Absent any motivation by one of ordinary skill to resort to the Alstermark disclosure. it is clear that a *prima facie* case of obviousness has not been generated in this case. Reconsideration and withdrawal of the outstanding obviousness rejection is accordingly respectfully requested.

IV. DOUBLE PATENTING

Claims 1-10 and 14-26 stand rejected on alleged obviousness-double patenting grounds over claims 1-30 of Alstermark. That rejection is respectfully traversed for the same reasons argued above with regard to the obviousness rejection. The claims of the present case are not obvious in light of the **claims** of Alstermark. A person of ordinary skill would not have been motivated to arrive at the presently claimed invention based on the Alstermark claims because, in the present claims, when *"D"* represents either H or OH, then at least one of R^{5a} and R^{5b} represents C_{1-3} alkyl or at least one of R^2 and R^3 is other than H or C_{1-4} alkyl. The **claims** of Alstermark do not lead one of ordinary skill to such compounds or render such compounds obvious. Withdrawal of the obviousness-type double patenting rejection is respectfully requested.

IV. SPECIFICATION

A minor typographical error has been corrected on page 2 of the specification. No new matter is entered.

Allowance of the application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

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Attachment: *Advanced Organic Chemistry* 3rd Ed., J. March, John Wiley and Sons, New York (1985), page 1100, and copies of the cover pages.

VERSION WITH MARKINGS SHOWING CHANGES MADE

IN THE SPECIFICATION

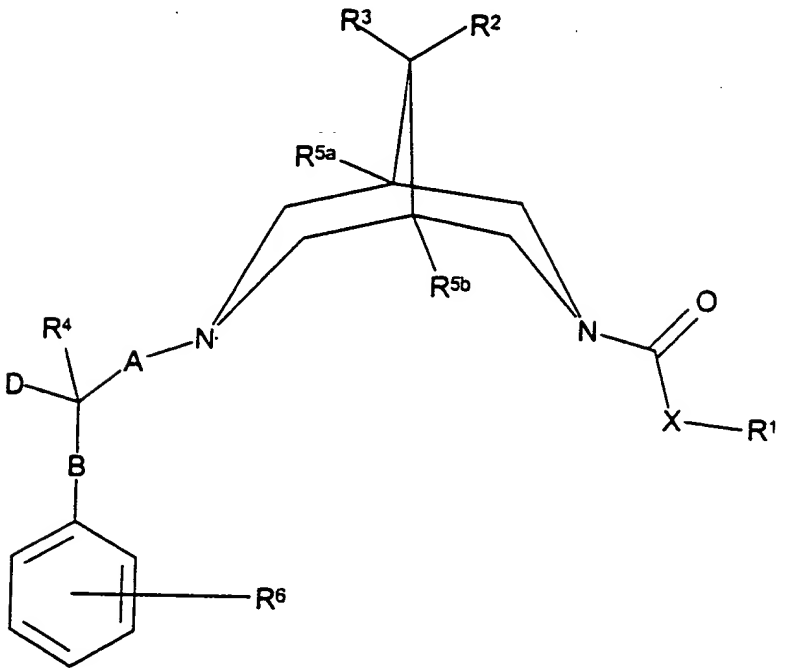
Please enter the following amended paragraph at page 2 lines 13-28 for corresponding paragraph previously presented. A copy of the amended paragraph showing the requested revisions is attached.

Antiarrhythmic drugs based on bispidines (3,7-diazabicyclo[3.3.1]nonanes), are known from *inter alia* international patent application WO 91/07405, European patent applications 306 871, 308 843 and [655 228] 665 228 and US patents 3,962,449, 4,556,662, 4,550,112, 4,459,301 and 5,468,858, as well as journal articles including *inter alia* J. Med. Chem. **39,** 2559, (1996), Pharmacol. Res., 24, 149 (1991), Circulation, **90,** 2032 (1994) and Anal. Sci. **9,** 429, (1993). Known bispidine-based antiarrhythmic compounds include bisaramil (3-methyl-7-ethyl-9α,4'-(Cl-benzoyloxy)-3,7-diazabicyclo[3.3.1]nonane), tedisamil (3',7'-bis(cyclopropylmethyl)spiro-(cyclopentane-1,9')-3,7-diazabicyclo[3.3.1]nonane), SAZ-VII-22 (3-(4-chlorobenzoyl)-7-isopropyl-3,7-diazabicyclo[3.3.l]nonane), SAZ-VII-23 (3-benzoyl-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane), GLG-V-13 (3-[4-(1H-imidazol-1-yl)benzoyl]-7-isopropyl-3,7-diazabicyclo[3.3.1]nonane), KMC-IV-84 (7-[4'-(1*H*-imidazolo-1-yl)benzenesulfonyl]-3-isopropyl-3,7-diaza-bicyclo[3.3.1]nonane

dihydroperchlorate and ambasilide (3-(4-aminobenzoyl)-7-benzyl-3,7-diazabicyclo[3.3.1]nonane).

IN THE CLAIMS

1 (Amended). A compound of formula I,



I

wherein

R^1 represents C_{1-12} alkyl, $-(CH_2)_a$-aryl, or $(CH_2)_aHet^1$ (all of which are optionally substituted [and/or terminated (as appropriate)] by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy);

a represents 0, 1, 2, 3, or 4;

Het[1] represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

X represents O or S;

R^{5a} and R^{5b} independently represent H or C_{1-3} alkyl;

R^2 and R^3 independently represent H, C_{1-4} alkyl (optionally substituted [and/or terminated] with one or more nitro or cyano groups), OR^7, $N(R^{7a})R^{7b}$, $OC(O)R^8$ or together form $-O-(CH_2)_2-O-$, $-(CH_2)_3-$, $-(CH_2)_4-$ or $-(CH_2)_5-$;

R^7 and R^8 independently represent H, C_{1-6} alkyl or $-(CH_2)_b$-aryl (which latter two groups are optionally substituted [and/or terminated] by one or more substituents selected from -OH, halo, cyano, nitro, C_{1-4} alkyl and/or C_{1-4} alkoxy);

R^{7a} and R^{7b} independently represent H or C_{1-6} alkyl;

b represents 0, 1, 2, 3 or 4;

R^4 represents H or C_{1-6} alkyl;

D represents H, [C_{1-4} alkyl,] -OH, or $-(CH_2)_cN(R^{10})(R^{11})$;

c represents 0, 1, 2, 3 or 4;

R^{10} represents H, C_{1-6} alkyl, $-(CH_2)_d$-aryl, $-C(NH)NH_2$, $-S(O)_2R^{13}$, $-[C(O)]_eN(R^{14})(R^{15})$, $-C(O)R^{16}$ or $-C(O)OR^{17}$;

e represents 1 or 2;

R^{11} represents H, C_{1-6} alkyl, $-C(O)R^{18}$ or $-(CH_2)_f$-aryl (which latter group is optionally substituted [and/or terminated (as appropriate)] by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

R^{14}, R^{15}, R^{16}, R^{17} and R^{18} independently represent H, C_{1-6} alkyl, Het^2 or $-(CH_2)_g$-aryl (which latter three groups are optionally substituted [and/or terminated (as appropriate)] by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

R^{13} represents C_{1-6} alkyl, aryl or $-(CH_2)_h$-aryl (all of which are all optionally substituted [and/or terminated (as appropriate)] by one or more substituents chosen from halo, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

d, f, g and h independently represent 0, 1, 2, 3 or 4;

Het^2 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R^6 represents one or more optional substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl (optionally terminated by $-N(H)C(O)OR^{18a}$), C_{1-6} alkoxy, $-C(O)N(H)R^{19}$, $-NHC(O)N(H)R^{20}$, $-N(H)S(O)_2R^{21}$ and/or $-OS(O)_2R^{22}$;

R^{19} and R^{20} independently represent H or C_{1-6} alkyl;

R^{18a}, R^{21} and R^{22} independently represent C_{1-6} alkyl;

A represents a single bond, C_{1-6} alkylene, $-N(R^{23})(CH_2)_j$-, $-O(CH_2)_j$- or $-(CH_2)_JC(H)(OR^{23})(CH_2)_k$- (in which latter three groups, the $-(CH_2)_j$- group is attached to the bispidine nitrogen atom, and which latter four groups are all optionally substituted by one or more OH groups);

B represents a single bond, C_{1-4} alkylene, $-(CH_2)_mN(R^{24})$-, $(CH_2)_mS(O)_n$-, $-(CH_2)_mO$- (in which three latter groups, the $\sim(CH_2)_m$- group is attached to the carbon atom bearing D and R^4), $-C(O)N(R^{24})$- (in which latter group, the -C(O)-

group is attached to the carbon atom bearing D and R^4), $N(R^{24})C(O)O(CH_2)_m$- or $-N(R^{24})(CH_2)_m$- (in which latter two groups, the $N(R^{24})$ group is attached to the carbon atom bearing D and R^4);

j, k and m independently represent 0, 1, 2, 3 or 4;

n represents 0, 1 or 2;

R^{23} represents H, C_{1-6} alkyl or

R^{24} represents H or C_{1-6} alkyl;

R^{25} represents H, C_{1-6} alkyl, Het^3 or $-(CH_2)_p$-aryl (which latter two groups are optionally substituted [and/or terminated (as appropriate)] by one or more substituents selected from -OH, cyano, halo, amino, nitro, C_{1-6} alkyl and/or C_{1-6} alkoxy);

Het^3 represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

p represents 0, 1, 2, 3 or 4;

or a pharmaceutically acceptable salt, solvate or protected derivative thereof[.];

provided that:

(a) when D represents either H or -OH, and R^{5a} and R^{5b} both represent H, then at least one of R^2 and R^3 represents OR^7, $OC(O)R^8$ or C_{1-4} alkyl, which alkyl group is substituted [and/or terminated] with one or more nitro or cyano groups; and

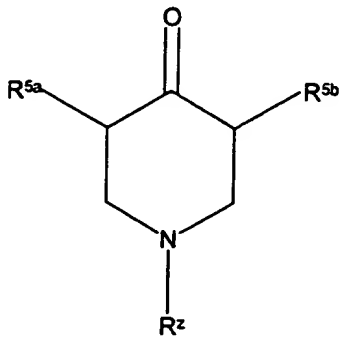
(b) when D represents -OH or $-(CH_2)_cN(R^{10})R^{11}$ in which c represents 0, then:-

(i) A does not represent $-N(R^{23})(CH_2)_j-$, $-O(CH_2)_j-$ or $-CH_2)_JC(H)(OR^{23})(CH_2)_k-$ (in which k is 0); and/or

(ii) m does not represent 0 when B represents $-(CH_2)_mN(R^{24})-$, $-(CH_2)_mS(O)_n-$ or $-(CH_2)_mO-$.

23 (Amended). A compound of formula IV as defined in Claim 21, or a protected derivative thereof, provided that when R^{5a} and R^{5b} both represent H, then at least one of R^2 and R^3 represents OR^7, $OC(O)R^8$ or C_{1-4} alkyl, which alkyl group is substituted [and/or terminated] with one or more nitro or cyano groups.

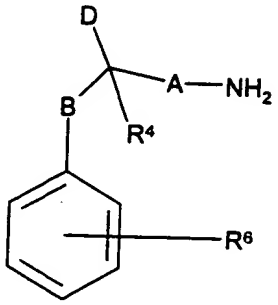
26 (Amended). A process for the preparation of a compound of formula VIII[, XVII, XVIII or XXVIII], as defined [herein] in Claim 24, or a compound of formula XVII, as defined in Claim 25, which comprises reaction of a compound of formula XXIX,



XXIX

wherein R^Z represents H or -C(O)XR^1 and R^1, R^{5a}, R^{5b} and X are as defined in Claim 1 with [(as appropriate) either:

(1)] a compound of formula XXX,



XXX

or a protected derivative thereof, wherein R^4, R^6, A, B and D are as defined in Claim 1[; or

(2) NH_3 (or a protected derivative thereof)], in all cases in the presence of a formaldehyde.